CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

OXAMYL

Chemical Code # 001910, Tolerance # 00303
SB 950 # 224

December 10, 1986
Revised 6/22/87; 10/24/88; 11/30/89; 10/23/92; 5/4/98

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect.
Chronic toxicity, dog:	No data gap, no adverse effects.
Oncogenicity, rat:	No data gap, no adverse effects.
Oncogenicity, mouse:	No data gap, no adverse effects.
Reproduction, rat:	No data gap, no adverse effects.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome effects:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time, however, inadequate chicken study on file.[1]

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[1] A study on cholinesterase inhibition in rats is on file.
Toxicology one-liners are attached.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T980504
Revised by H. Green, 12/13/90 and T. Kellner, 10/23/92, Gee, 5/4/98

Record numbers through -094:098858 have been examined.
These pages contain summaries only. Each individual worksheet may contain additional effects.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED (ONCOGENICITY + CHRONIC), RAT

**** 303-091 089673** Malley, L. "Combined Chronic Toxicity/Oncogenicity Study with Oxamyl (IN D1410-196) Long-Term Feeding Study in Rats", (E. I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE., Report # 278-91, 7/11/91) Oxamyl, 97.1% purity, was fed in the diet to 62 Crl:CD®BR rats/sex/group at 0 (control), 25, 50, 100, and 150 ppm for 24 months. Body weight differences (5%-29% less than control) and increased hyperreactivity in both sexes at 100 and 150 ppm was reported. **Possible adverse effect:** Increase in photoreceptor cell atrophy in females at 150 ppm from days 379 to terminal sacrifice. Chronic NOEL = 50 ppm (reduced body weights and plasma ChE inhibition at 100 and 150 ppm). **No oncogenic effects. Acceptable**. (Green, Kellner and Gee, 10/9/92).

CHRONIC TOXICITY, RAT

003 031158, "Long-Term Feeding Study in Rats and Dogs with 1-(Dimethylcarbamoyl)-N-(Methylcarbamoyloxy)-Thioformimidic Acid, Methyl Ester (IND-1410): Final Report", (Haskell Laboratory, MRP # MR-1203, HLR # 37-72, 2/72). Formulated oxamyl (93.5% final) Fed at 0, 50, 100 or 150 ppm for 2 years in diet of 72 male and 56 female (0 ppm) or 36 male and 20 female (50 - 150 ppm) rats/group; 6 rats/sex/group sacrificed at 12 months; MTD indicated by decrease in weight gain at 150 ppm - 15% in male and 37% in female; no adverse effect indicated; **UNACCEPTABLE** and not upgradeable (no analysis of diet, insufficient histopathology, insufficient clinical chemistry, no ophthalmological examinations, insufficient numbers of nulliparous females); A. Apostolou, 6/20/85; J. Gee, 6/5/86, 6/19/87; S. Morris, 9/6/88.
EPA one-liner: "Systemic NOEL = 50 ppm (LDT) (decreased body weight); ChE NOEL > 150 ppm (HDT); oncogenic NOEL > 150 ppm (HDT); Core grade: minimum.

062 042484, Pathology reports 6-72 (controls and high dose groups) and 33-80 (low and mid-dose groups) for 031158.

070 051072, Complete report with tables missing from 031158 and rebuttal for 031158.

CHRONIC TOXICITY, DOG

** 303-089 092560 Mebus, C. "Chronic Toxicity Study with Oxamyl (IN D1410-196) One-Year Feeding Study in Dogs", (E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE., Report # 381-90, 11/1/90). Oxamyl, 97.1% purity, was fed in the diet for 12 months at 0 (control), 50, 150, and 250 ppm to 5 Beagle dogs/sex/group. Increased incidence of diarrhea and vomiting was reported in both sexes at 150 and 250 ppm and in 50 ppm females. Reduced body weights (2%-22%) were noted in both sexes at 150 and 250 ppm. **No Adverse effects indicated**. Chronic NOEL = 50 ppm (tremors and vomiting at 150 and 250 ppm). **Acceptable**. ChE NOEL of 50 ppm was indicated by supplemental study -094:098858. Green, Kellner and Gee, 10/5/92.

-094 098858 Dickrell, L. "52-Week Dietary Toxicity Study with IND-1410 (Oxamyl) in Male Dogs", (Hazleton Laboratories America, Inc., Madison, WI. 53704, Report # 555-90, 10/3/91). Oxamyl, 97.1% purity, was fed in the diet to 5 male Beagle dogs per group at 0 (control), 12.5, 20.0, 35.0, and 50.0 ppm for 52 weeks. Clinical signs, body weights, food consumption, hematology, clinical chemistry, and macroscopic findings were unremarkable. Chronic NOEL = 50 ppm. ChE NOEL = 50 ppm. **Supplemental.** Green, Kellner and Gee, 10/1/92.

003 031157, "Long-Term Feeding Study in Rats and Dogs With 1-(Dimethylcarbamoyl)-N-(Methylcarbamoyloxy)-Thioformimidic Acid, Methyl Ester(IND-1410): Final Report", (Haskell Laboratory, MRP # MR-1203, HLR # 37-72, 2/72) Formulated oxamyl (93.5% final); 0, 50, 100 or 150 ppm in diet for 2 years to 4 dogs/sex/group; no dose-related clinical signs or pathological abnormalities; inconclusive elevation of serum cholesterol and alkaline phosphatase; no adverse effect indicated; **UNACCEPTABLE** and not upgradeable (no justification of dose levels, MTD not demonstrated; inadequate histopathology data, intercurrent disease, age of dogs, no analyses of diet, no ophthalmologic examinations); initial review indicated a possible adverse effect (hepatotoxicity), A. Apostolou 6/20/85; rereview of complete submission indicated no adverse effect; J. Gee, 6/4/86, 6/19/87; S. Morris 9/6/88.
EPA one-liner: Systemic NOEL = 100 ppm; Core grade: Minimum.

062 042485, Pathology reports 8-72 and 34-80 for 031157.

070 052065, Complete report and rebuttal for 031157.

082 073981, "One-year Feeding Study With Oxamyl in Dogs - Possible "Unreasonable Adverse Effect" Disclosure" (Haskell Laboratory, 5/89). Two page letter to EPA concerning findings in currently ongoing dog chronic toxicity study. This is the dog chronic toxicity study referred to in the registrant's letter dated March 21, 1988.

ONCOGENICITY, RAT

003 031158, "Long-Term Feeding Study in Rats and Dogs with 1-(Dimethylcarbamoyl)-N-(Methylcarbamoyloxy)-Thioformimidic Acid, Methyl Ester (IND-1410): Final Report", (Haskell Laboratory, MRP # MR-1203, HLR # 37-72, 2/72). Formulated oxamyl (93.5% final). Fed at 0, 50, 100 or 150 ppm for 2 years in diet of 72 male and 56 female (0 ppm) or 36 male and 20 female (50 - 150 ppm) rats/group; 6 rats/sex/group sacrificed at 12 months; MTD indicated by decrease in weight gain at 150 ppm - 15% in male and 37% in female; no adverse effect indicated; **UNACCEPTABLE** and not upgradeable (no analysis of diet, insufficient histopathology, insufficient numbers of nulliparous females). A. Apostolou, 6/20/85; J. Gee, 6/5/86, 6/19/87; S. Morris, 9/6/88.
EPA one-liner: "Systemic NOEL = 50 ppm (LDT) (decreased body weight); ChE NOEL > 150 ppm (HDT); oncogenic NOEL > 150 ppm (HDT); Core grade: minimum.

NOTE: In a letter dated March 21, 1988, the registrant committed to submit a new rat oncogenicity study in December, 1991.

ONCOGENICITY, MOUSE

** 062-066 042486-042490, "Long Term Feeding Study in Mice With Oxamyl", (WIL, Project #

WIL-77033, 3/9/81). Oxamyl (97.1%); fed in the diet at 0, 25, 50 or 100/75 ppm for 2 years; 80/sex/group; no oncogenic or chronic effects reported; nominal systemic NOEL = 25 ppm (decreased weight gain), oncogenic NOEL $\geq$ 75 ppm (nominal - analyses of diets show that << 75 ppm usually found); initially reviewed as unacceptable but upgradeable with submission of analyses of diet samples. These have been submitted in Record # 51073. The study is upgraded to **ACCEPTABLE** status. J. Gee, 6/5/86.
EPA one-liner: "Oncogenic NOEL> 75 ppm (HDT); Core grade: minimum.

070 051073, Purity, stability, diet analyses and rebuttal to 042486.

REPRODUCTION, RAT

** 303-088 088993 Hurtt, M. "Reproductive and Fertility Effects with Oxamyl (IN D1410) Multigeneration Reproduction Study in Rats", (E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE., Report # 423-90, 10/16/90). Oxamyl technical (97.1% purity, lot #7577-46) was fed in the diet to 30 Crl:CD*BR rats/sex/group for 2 generations (one litter/generation) for 74 and 105 days before mating to F0 and F1 adults, respectively, at 0 (control), 25, 75, and 150 ppm. Reduced body weights were noted in F0 and F1 parental males (5% - 38% decrease) and females (6% - 35% decrease) at 75 and 150 ppm. Reduced food consumption was indicated for F0 and F1 males at 75 and 150 ppm. Increased incidence of skin sores (F0 males and F1 males and females at 150 ppm), hyperreactivity (F1 males and females at 75 and 150 ppm) and alopecia (F1 females at 75 and 150 ppm) was reported in adults. **No Adverse Reproductive Effects. Parental NOEL = 25 ppm** (reduced body weights and food consumption at 75 and 150 ppm). Reduced viability index at maternotoxic dose levels of 150 ppm. **Reproductive NOEL = 25 ppm.** (reduced pup weights and pup weight gain at 75 and 150 ppm). **Acceptable**. (Green, Kellner and Gee, 10/1/92).

003 979401, "Long-Term Feeding Study in Rats and Dogs With 1-(Dimethylcarbamoyl)-N-(Methylcarbamoyloxy)-Thioformimidic Acid, Methyl Ester (IND-1410): Final Report", (Haskell Laboratory, MRP # MR-1203, HLR # 37-72, 02/02/72). Formulated oxamyl (93.5% final). Fed at 0, 50, 100 or 150 ppm in the diet of 16 rats/sex/group; each female mated with 3 males/generation; 3 generations, 2 litters/generation; necropsy on 2, 21-day-old F_3b pups/litter; nominal pup NOEL = 50 ppm (decreases in live pups/litter and viability at days 4 and 12 at nominal doses of 100 and 150 ppm); paternal NOEL = 100 ppm (16% decrease in body weight of F_0 males by day 168 at 150 ppm), maternal NOEL = 50 ppm (16% decrease in body weight of F_0 females by day 168 at 100 ppm); **possible ADVERSE EFFECT** indicated (pup NOEL $\leq$ parental NOEL's); study **UNACCEPTABLE** and not upgradeable (no analysis of dosing material, no interim pup weights, inadequate data on observations of parental animals, individual data on pups missing, no data on food consumption, lack of sufficient numbers of necropsied pups, pairing of each female with three males per generation, no parental histopathology); A. Apostolou, 6/20/85; J. Gee, 7/3/86; S. Morris, 9/1/88.
EPA one-liner: "Fetotoxic NOEL = 50 ppm (LDT) (decreased weanling body weights); reproductive NOEL = 50 ppm (LDT) (lowering of the viability and lactation indices); Core grade: minimum.

067 042491-92, Supplemental to 979401 (Individual weanling body weights, mating schedules, reproduction performance.)

070 050994, Data on purity and stability of test material and rebuttal to 979401.

NOTE: In a letter dated March 21, 1988, the registrant committed to submit a new rat reproduction study in January, 1991. This study, dated 10/16/90, was submitted to MT DPR and was found to be acceptable (see -088:088993). This study indicated that oxamyl was generally negative for reproductive effects. A significant decrease in pup viability was seen at 150 ppm, but this was not flagged as an adverse reproductive effect because of marked maternotoxicity seen at 100 and 150 ppm. A parental NOEL of 25 ppm was established because of alopecia, hyperreactivity, reduced body weights and food consumption at 75 and 150 ppm. T. Kellner, 10/23/92.

TERATOLOGY, RAT

** 081 072151 "Teratogenicity Study of IN D1410-196 in the Rat" (Haskell Laboratory, Project ID 473-88, 10/3/88). Oxamyl, 97.2%, was administered by oral gavage to Crl:CD BR rats at 0 (distilled water vehicle control), 0.20, 0.50, 0.80 or 1.50 mg/kg on days 7-16 of gestation. Decreased maternal food consumption, reduced maternal weight, and transient tremors were observed at 0.80 and 1.50 mg/kg/day. Delayed fetal development was elevated at all treatment levels, and decreased fetal weight was noted at 0.50, 0.80, and 1.50 mg/kg/day. Reproductive parameters and malformation rates were unaffected by treatments. Maternal NOEL = 0.50 mg/kg (decreased food consumption and body weight; transient tremors). Developmental NOEL < 0.20 mg/kg (delayed fetal development). Developmental NOAEL = 0.20 (decreased fetal weight). Neither the delayed fetal development or decreased fetal weight are considered adverse health effects for risk assessment purposes. The study is **ACCEPTABLE**. D. Shimer, 7-14-89; G. Chernoff, 11/29/89.

003 979400, "Teratogenic Study in rats With S-Methyl-1-Dimethylcarbamoyl-N-(Methylcarbamoyl)Oxy) Thioformimidate (IND 1410)", (Haskell Laboratory, report no. 5-71 dated 1/71). Oxamyl (93.5%); fed in the diet at 0, 50, 100, 150 or 300 ppm, days 6-15 of gestation; approximately 26/group; no developmental effect reported; nominal maternal NOEL = 50 ppm (body weight); **UNACCEPTABLE** (inadequate report of test proceedings, no analyses of diets for actual content and stability during the test.) A. Apostolou, 6/20/85 (original review). J. Gee, 6/5/86.
EPA one-liner: Maternal NOEL = 50 ppm (LDT); fetotoxic NOEL = 300 ppm (HDT); teratogenic NOEL = 300 ppm (HDT). Core grade: (not given).

067 042493 Supplementary information to 979400 (Individual and group dam and fetal data.)

070 051074 Data on purity and stability and 3-page version of the protocol and rebuttal to 979400.

TERATOLOGY, RABBIT

** 058 017045, "Teratology Study in Rabbits: Oxamyl: Final Report", (10/1/1980, Hazleton Laboratory, report no: 201-545, 10/1/80). Oxamyl, 97.1%, given by oral gavage to New Zealand white rabbits, 13-17 per group at 0, 1, 2 or 4 mg/kg, days 6-19; teratogenic NOEL $\geq$ 4 mg/kg, fetotoxic NOEL $\geq$ 4 mg/kg, maternal NOEL = 1 mg/kg (decreased food consumption and decreased weight gain, days 6-19); initially reviewed as unacceptable (dose selection not justified with no evidence of maternal toxicity, no analysis of dosing solution provided.) Record no. 51075 contains the analyses of dosing solution for days one and two and the results of a

pilot study justifying the dose selection.Upgraded to **ACCEPTABLE** status. A. Apostolou, 6/21/85 and J. Gee, 6/22/87.
EPA one-liner: Teratogenic NOEL = > 4 mg/kg/day (HDT); fetotoxic NOEL = 2 mg/kg/day; Core grade: minimum. [Fetotoxic value apparently based on slight (not statistically significant) increase in resorptions and decrease in fetal viability at 4 mg/kg.]

070 051075, Data on dosing analyses and results of a pilot study plus rebuttal for 017045.

GENE MUTATION

003 979403, "Oxamyl Mutagenicity Study Using Bacteria (S. typhimurium and E. coli", (Institute of Environmental Toxicology - Japan, 6/4/76). Three-line summary of a study in Salmonella with negative findings reported. A. Apostolou, 6/20/85.

** 058 017044, "Mutagenicity Evaluation of Oxamyl in Salmonella typhimurium", (Haskell Laboratory, Report No. 614-81, 10/5/81). Oxamyl, 97.1%; tested in Salmonella strains TA1535, TA1537, TA98 and TA100 with and without activation, at 0, 50, 100, 500, 1000, 5000 or 10,000 ug/plate, duplicate plates, two trials. No evidence for increase in reversion rate. **ACCEPTABLE**. A. Apostolou, 6/21/85.

** 058 017043, "Chinese Hamster Ovary Cell Assay for Mutagenicity", (Haskell Laboratory, Report No. 265-82, 3/10/82). Oxamyl, 97.1%; Chinese hamster ovary cells, CHO-K1; tested without activation at 0, 50, 200, 1000 or 1200 uM in duplicate (trial 1), at 0, 50, 200, 500, 750 or 1000 uM (trial 2); with activation, tested at 0, 25, 100, 200, 300 or 500 uM (trial 1) and 0, 25, 100, 300, 500 or 700 uM (trial 2) in duplicate cultures; no consistent evidence for mutagenicity; **ACCEPTABLE**. A. Apostolou, 6/21/85.

CHROMOSOME MUTATION

** 058 017042, "Mutagenicity Evaluation of H #14190 in an In vitro Cytogenetic Assay Measuring Chromosome Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells", (Litton Bionetics Project No. 20990, 4/82). Oxamyl, tested with activation for 2 hours at 0, 2.3, 7.0, 23.3, 70.0, 233.0 or 700 ug/ml (700 was toxic) followed by further incubation for 8 to 10 hours and tested without activation for 8.5 to 10 hours at 0, 2.3, 7.0, 23.3, 70.0 or 700 ug/ml in trial 1 and 0, 12.5, 25.0, 50.0, 75 or 100 ug/ml in trial 2; in the first trial without activation, an incidence of 8 dicentrics as found at 2.3 ug/ml - this was not repeated in the second trial; scored 100 cells per concentration; initially reviewed as unacceptable (no repeat trial, concentration selection) Reconsideration of the study finds that, in fact, a confirming repeat trial without activation was performed and the concentrations in the second trial were all higher than the one at which the positive effect was reported in the first trial. Based on these factors, the study is upgraded to **ACCEPTABLE** with minor deficiency noted as a single harvest time of about 12 hours. A. Apostolou, 6/24/85 and J. Gee, 6/22/87.

DNA DAMAGE

003 038180, Very brief summary of results of three bacterial mutation assays. A. Apostolou, 6/21/85.

** 058 017041, "Unscheduled DNA Synthesis/Rat Hepatocytes In Vitro." (Haskell Laboratory, Report No. 719-82, 11/11/82) Oxamyl, 97.1%, tested with primary rat hepatocytes at 0, 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2}, 0.1, 1, 5 or 10 mM, 18 hours, two cultures, two trials; 50 nuclei were scored for one slide, 25 for the second slide in trial one; in trial two, a single culture and 25 nuclei scored to confirm results; no evidence for unscheduled DNA synthesis by autoradiography; **ACCEPTABLE**. A. Apostolou, 6/24/85. [Study was initially considered unacceptable but reconsideration by J. Gee, 12/9/86, finds that the objections were not sufficient for rejection.]

NEUROTOXICITY

007 979394, "IND-1410 Delayed Paralysis Test (Adult white Leghorn Chickens) Single Oral Administration With a 28 Day Recovery Period", (Haskell Laboratory, 6/4/70). Oxamyl (no purity stated); given by oral gavage at 20 or 40 mg/Kg; 5 hens/group; atropine protected; no evidence of delayed neuropathy; **UNACCEPTABLE** (inadequate number of animals, no repeat dosing, no individual animal data), NOT UPGRADEABLE. A. Apostolou, 6/20/85 (original review of summary). J. Gee, 6/5/86.
EPA one-liner: LD_{50} = 40 mg/kg; 0.5 mg/kg of atropine was effective in protecting against the LD_{50}. No compound related histopathological changes reported. Core grade: (not given).

067 042494, Supplemental information to 979392 and 979394; pathology report.

070 051076, Duplicates of 979394 and 979392 and rebuttal to 979394.

007 979392, Range-finding study for 979394.

253-271; 159979; “Reversibility Study with Carbamate Insecticides in Rats”; (L.A. Malley; E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Study No. HL-1997-00641; 11/10/97); Forty rats/sex/group were orally gavaged with 0 or 1 mg/kg of oxamyl technical (purity: 98.3%) or 0 or 3 mg/kg of methomyl technical (purity: 98.6%). Plasma, rbc, and brain cholinesterase (ChE) activities were measured for 10 animals/sex/group at 30 minutes and 2, 3 and 4 hours post-dose. Tremors were noted at 30 minutes post-dose in animals treated with both of the test materials. This sign was not evident at 2 hours after dosing. For the oxamyl treated animals, at 30 minutes after dosing, plasma, rbc and brain ChE activities were significantly inhibited (plasma: (M) 43%, (F) 50% of control; rbc: (M) 42%, (F) 39% of control; brain: (M) 55%, (F) 52%). By two hours, ChE activity had returned to control levels. Likewise, for the methomyl treated animals, at 30 minutes post-dose, plasma, rbc and brain ChE activities were significantly inhibited (plasma: (M) 73% of control; rbc: (M) 44%, (F) 59% of control; brain: (M) 54%, (F) 61% of control). By 2 hours, the ChE activities had returned to control levels. Study data indicate that significant ChE inhibition is largely reversible by 2 hours after dosing for both of the test materials. **Possible adverse effect indicated:** tremors and significant brain cholinesterase inhibition evident. **NOEL:** (oxamyl) < 1 mg/kg, (methomyl) < 3 mg/kg; **Study supplemental.** (Moore, 3/26/98)